Exhibit A

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

GENERAL ADVICE

Teva Pharmaceuticals USA, Inc.
Attn: John Derstine
Director, Regulatory Affairs, US Generics
john.derstine@tevapharm.com

Dear Sir or Madam:

This letter is to inform applicants with an approved or pending application for an angiotensin II receptor blockers (ARB) drug product (DP), as well as holders of related drug master files(DMFs), of FDA concerns related to the presence of one or more toxic impurities in some ARB drugs. This general advice letter summarizes FDA findings to date and provides recommended actions to take to ensure that your drug product, drug substance/active pharmaceutical ingredient (API), and raw materials are absent of these impurities or below our recommended limit.

Background

In June 2018, FDA was informed of the presence of an impurity, identified as N-Nitrosodimethylamine (NDMA), from one valsartan API producer. Since then, FDA has determined that other types of nitrosamine compounds, e.g., N-Nitrosodiethylamine (NDEA), are present at unacceptable levels in APIs from multiple API producers of valsartan and other drugs in the ARB class. FDA has and will continue to provide periodic updates on this problem on its website (https://www.fda.gov/drugs/drugsafety/ucm613916.htm). FDA continues to collaborate with other drug regulatory agencies around the world to address this problem, and FDA is committed to working with manufacturers and applicants impacted by this problem to bring this to a full and timely resolution. FDA and other regulators, as well as many manufacturers, have developed and are using methods validated to detect and quantify a variety of nitrosamine impurities. FDA has posted these methods on its website. FDA has also issued Information Request letters to application and DMF holders to request specific information and samples of drugs thought to be at risk for the presence of a nitrosamine impurity.

Nitrosamine compounds are potent genotoxic carcinogens in several nonclinical species and are classified as probable human carcinogens by the International Agency for Research on Cancer (IARC). In fact, "N-nitroso" compounds are identified as a "cohort of concern" in internationally harmonized guidance, ICH M7, *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk*. ICH M7 recommends that known mutagenic carcinogens, such as nitrosamines, be controlled at or below the acceptable cancer risk level. Due to their known potent carcinogenic effects, and because it is feasible to limit these impurities by taking reasonable steps to prevent or eliminate their

presence, FDA has determined that there is no acceptable specification for nitrosamines in ARB API and DP. Therefore, FDA advises that nitrosamines should be absent (i.e., not detectable as described below) from ARB API and ARB drug products. As an initial measure, FDA published "interim acceptable limits" for these nitrosamine impurities in ARBs. ARB DS or DP with levels of impurities exceeding these interim limits were recommended for recall from the market. FDA has used the interim limits to guide immediate decision-making for product recalls to balance the risks of potential long term carcinogenic risk and disruption to clinical management of patients' hypertension and heart failure. FDA is now seeking the information outlined below to ensure that ARB API and DP entering the marketplace have no detectable nitrosamines.

Recent information gathered by FDA suggests several general causes of the presence of a nitrosamine impurity in ARB APIs. First, we now know that nitrosamine impurities can form during API processing under certain processing conditions and in the presence of some types of raw materials and starting materials. These materials include intermediates that are not purged in subsequent steps of the API process. A second cause appears to be from the use of contaminated raw materials used in the manufacturing process. Recovered materials, such as recovered solvents and catalysts, may pose a risk for nitrosamine formation due to the presence of amines in the solvents or catalysts sent for recovery and the subsequent quenching of these materials with nitrous acid to destroy residual azide without adequate removal. Independent recovery facilities may co-mingle solvents/catalysts from various customers or not perform adequate cleaning of equipment between customers. A similar cause may be from contaminated starting materials, including intermediates supplied by a vendor, that use processing methods or raw materials causing formation of nitrosamines in their material. Contamination from vendor-sourced raw materials and starting materials/intermediates is particularly challenging because an API producer whose process is not capable of forming a nitrosamine compound may not realize their process is at risk to the presence of such impurities. FDA is aware that some ARB producers have identified a nitrosamine in their finished API, even though they are using processes incapable of forming a nitrosamine impurity.

The multiple causes listed above can occur in the same API process. The typical tests for API purity, identity, and known impurities are unlikely to detect the presence of a nitrosamine impurity. Further, each failure mode could result in different nitrosamines, different amounts, or undetectable amounts of nitrosamine impurities in different batches from the same process and API producer.

Accordingly, FDA advises:

1. ARB DP manufacturers test representative samples of each drug product batch, or alternatively a representative sample of each API lot used in each drug product batch, they have produced for the US market to determine whether any contain a detectable amount (defined below) of a nitrosamine impurity. Testing should include DP batches already distributed that have not yet reached their labeled expiration date as well as those not yet distributed by the DP manufacturer. Any DP batch already in distribution, as of the date of this letter, with a nitrosamine level that exceeds the FDA published interim acceptable limit should be recalled, if distributed, or quarantined pending appropriate disposition if not distributed. Any DP product batch found to contain a detectable nitrosamine impurity that is

below the interim acceptable limit should not be released by the DP manufacturer for distribution unless FDA agrees that distribution is warranted to prevent or mitigate a shortage of a medically necessary drug (or if for export from the US, a shortage determination was made by the importing country's national regulatory agency).

2. ARB DP manufacturers test representative samples of each API batch in their possession to demonstrate the absence of nitrosamines prior to use in DP manufacturing. In addition, DP manufacturers should test each API lot received from each supplier before releasing the API for use until the DP manufacturer has verified that the supplier can consistently produce API without a detectable nitrosamine (as defined below) in accordance with the CGMP regulations at 21 CFR 211 subpart E; see also FDA guidance for industry, ICH Q10, *Pharmaceutical Quality System*.

3. ARB applicants (or DP manufacturers on their behalf) report to FDA a finding of detectable nitrosamine in either an API lot or in a DP batch whether or not distributed. The Field Alert Report (FAR) regulation for ANDAs and NDAs (21 CFR 314.81) requires such reports for distributed batches. If not distributed, reporting a finding of detectable nitrosamine to the FAR system will assist FDA in timely remediation. For instructions on submitting a FAR, please refer to the draft guidance document *Field Alert Report Submission: Questions and Answers Guidance for Industry* at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM613753.pdf.

4. Applicants report to FDA a summary of the testing performed, as requested above, for the presence of any nitrosamine impurities in batches distributed in the US or exported from the US that are within their labeled expiration, even if recalled. We request a table be submitted to each application, if not already provided in previous correspondence to the application, with the following information for each batch number that is sampled and tested:
    - product name (identify whether API or DP batch)
    - labeled strength (if DP batch)
    - date of manufacture
    - labeled expiration date
    - name of test method
    - amount and type of nitrosamine detected, if any, or "none detected."

    Data should be submitted to the application as a "General Correspondence;" the words "nitrosamine-related" should be prominently displayed on the cover letter.

5. Applicants of pending ARB applications should provide a written statement as General Correspondence declaring that the API supplier provides API that does not contain any detectable nitrosamine impurities. No further action in response to this letter is needed if this information has already been submitted to the application or referenced DMF.

6. ARB API producers test representative samples of each batch of an ARB API to determine whether any contain detectable nitrosamine impurities. Testing should include API batches distributed and within expiry, labeled with a 'retest by' date, and those not yet distributed. Any API batch containing a nitrosamine impurity above the interim acceptable limits should

be recalled, if distributed, or dispositioned as not suitable for use in DP intended for the US market. If detected below the interim acceptable limit, the batch should not be distributed for use in DP intended for the US market unless FDA agrees that such use is warranted to prevent or mitigate a US shortage of a medically necessary drug.

7. API batches may be reprocessed, reworked, and/or reconditioned to be rendered absent of a detectable nitrosamine impurity as provided for in existing policies for amending or supplementing and controlling such operations. If a batch is found to contain nitrosamines and is reprocessed or reworked in any way, this should be reported to the DMF and/or application. Please note that such amendments may have user fee goal date implications and will be assessed accordingly.

8. ARB API producers evaluate each process for the potential to form a nitrosamine impurity and if at risk, make changes necessary to prevent nitrosamine formation. If the process cannot be changed to prevent nitrosamine formation, FDA will permit use of a robust purging/elimination step(s) provided that it includes an appropriately sensitive test to verify that the resulting intermediate or API does not contain a detectable nitrosamine impurity. See existing FDA guidance in ICH Q7 *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*, ICH Q11 *Development and Manufacture of Drug Substances*, and ICH M7.

9. Batch testing to verify no detectable nitrosamine in the API should continue unless the API producer has demonstrated their process is not at risk for producing detectable nitrosamine in accordance with guidance (see, e.g., ICH Q7). This includes demonstrating that:
    - starting materials, including vendor-supplied intermediates, have no detectable nitrosamines or such amounts can be purged such that the API contains no detectable amounts of nitrosamines, and
    - raw materials used in the process, including recovered solvents and catalysts, contain no detectable amounts nitrosamines.

10. ARB API producers should voluntarily report the finding of a nitrosamine impurity to FDA in a Field Alert Report even if the contaminated material was not used in API processing. FDA will review the reports to determine if other API producers are unknowingly at risk to nitrosamine contamination and notify accordingly.

11. ARB API producers report to FDA a summary of the testing performed, as requested above, for the presence of any nitrosamine impurities in batches distributed in the US, whether directly as an API or after incorporation into a DP for the US, that are within their labeled expiration or retest-by date, even if recalled. We request a table be submitted to each DMF, if not already provided in previous correspondence to the DMF, with the following information for each batch number that is sampled and tested:
    - API name
    - date of manufacture
    - labeled expiration or retest-by date
    - name of test method

- amount and type of nitrosamine detected, if any, or "none detected."

Data should be submitted to the Drug Master File as "Quality/Controls;" the words "nitrosamine-related" should be prominently displayed on the cover letter.

12. ARB API producers report to each ARB DMF information about each independent facility that recovers materials used in ARB production for the past two years. We request the following information about such facilities: business name; address; name of recovered material; and, the month and year the recovery facility has been performing recovery operations for the ARB.

FDA will, to the extent possible, expedite review of amendments and supplements for manufacturing changes required to eliminate or limit a nitrosamine impurity, or when needed to prevent or mitigate a drug shortage.

For the testing requested in this letter, the detectable amount of nitrosamine impurity should be based on one of the following:

1. The limit of detection established in one of FDA's published methods.
2. A method published by another regulatory agency that is equivalent to FDA's method(s).
3. Any appropriately developed and validated method capable of a LOD and Limit of Quantitation (LOQ) equivalent to a method published by FDA.

The interim acceptable limits and FDA published methods, as well as other FDA information on this issue, are available at https://www.fda.gov/Drugs/DrugSafety/ucm613916.htm.

FDA published methods have been validated to detect and quantify NDMA and NDEA in all ARB APIs and some ARB DP formulations. FDA may update existing methods or post new methods once validated for use in detecting other nitrosamines in DPs and APIs. FDA may also update its published methods to improve their limits of detection and/or quantitation; if updated, FDA expects that manufacturers will update their methods to achieve comparable limits and apply the new LOD, if any, in making decisions about batch suitability.

You should share this letter with your suppliers (e.g., solvent recovery vendors and starting material suppliers) and contract manufacturers.

If you have any questions, please contact Rey Cantave at reynolds.cantave@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Paul Schwartz, Ph.D.
Division Director
Post Marketing Activities II
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Paul Schwartz

Digitally signed by Paul Schwartz
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